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10/727,172	12/03/2003	Amine Abina	034253-002	5982

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
10/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/727,172	ABINA, AMINE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8-19,23 and 26-38* is/are pending in the application.

4a) Of the above claim(s) *27-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 8-19, 23, 26,38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 7/24/07 has been entered. Claims 1-3, 5-7, 20-22, and 24-25 have been canceled and new claim 38 has been added. Claims 4, 8-19, 23, and 26-38 are now pending in the instant application. This application contains claims 27-37 drawn to an invention nonelected with traverse in the response filed on 12/5/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 4, 8-19, 23, 26, and 38 are therefore currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claims 4, 8-19, 23, 26, and 38 are objected to as comprising non-elected subject matter, there being no allowable genus claims. It is noted that the restriction/election requirement was made Final in the previous office and that the claims have been examined based on applicant's election of the species adenovirus as the first virus, adeno-associated virus as the second/additional virus, and cytokines (interleukins) as the heterologous protein. While the claims have been amended to limit the first virus to adenovirus, the claims continue to read broadly on heterologous proteins other than cytokines, and on second viruses other than adeno-associated viruses. The species elections however have previously been made FINAL and therefore the instant claims continue to be examined based on the elected species.

Claims 4, 8-18 are further objected to failing to depend on a preceding claim, see MPEP 608.01(n) and 37 CFR 1.75. Claims 4, and 8-18 depend on claim 19. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claims 1-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained over pending claims 4, 8-19, 23, 26, and 38, and withdrawn over canceled claims 1-3, 5-7, 20-22, and 24-25. Applicant's arguments and the declaration under 37 CFR 1.132 by Amine Abina have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that the claims have been amended to recite that the recombinant virus is an adenovirus and that the Declaration of Dr. Abina demonstrates that it would not have required undue experimentation to determine a tolerizing dose of the adenovirus effective in inhibiting formation of neutralizing antibodies and/or antigen presenting cells.

In response, the claims have been amended such that all claims depend on claim 19, which now recites a method of inhibiting formation of neutralizing antibodies directed against a heterologous protein comprising administering to the mammal a recombinant adenovirus or fragment thereof wherein the genome of the recombinant adenovirus or fragment comprises a nucleic acid sequence encoding the heterologous protein and regulatory sequences and wherein the recombinant adenovirus or fragment is administered in an amount sufficient to deplete or inhibit at least some antigen presenting cells of the mammal. While the amendment reduces the

scope of the claims to the elected species of adenovirus, the amendment does not overcome the rejection of record which was based on the lack of enabling disclosure for practicing the methods as claimed with a recombinant adenovirus encoding a heterologous protein such as a cytokine.

Regarding the Declaration by Dr. Abina, the declaration points to various sections of the specification as providing support for arriving at the preferred amounts of recombinant adenovirus for use in the invention. It is noted that the declaration states in particular that the amount of adenovirus particles to deplete or inhibit at least some antigen presenting cells of a mouse is equal to or greater to 10^{10} particles, citing page 13, paragraph 46 of the specification. In response, it is first noted that the claims are not limited to the administration of dosages of equal or greater to 10^{10} particles of recombinant adenovirus. Further, the disclosure of the specification regarding dosages was analyzed in detail in the previous office action and not found enabling for the breadth of the claims as written, which generally recite "an amount sufficient" to inhibit formation of neutralizing antibodies and deplete or inhibit at least some antigen presenting cells. Only claim 26, which has been amended to recite the use of equal to or greater than $8X10^9$ pfu/mouse, recites any specific dosage. However, the rejection of record discussed in detail the fact that at the time of filing, the administration of recombinant adenovirus for expressing encoded heterologous proteins in mammals was well known and well documented, as were the associated problems with recombinant adenovirus administration, such as the development of neutralizing antibodies against both adenoviral proteins and heterologous proteins encoded by recombinant adenoviruses. Abina et al., which includes as an author the instant inventor, provides a summary of the state of the prior art of neutralizing antibodies induced by recombinant adenoviruses and further provides a specific example which demonstrates that a

single dose of 6X10-9 pfu of a recombinant adenovirus encoding human TPO administered intravenously to mice produces cross-reactive neutralizing antibodies against human TPO (Abina et al, (1998), see IDS of 4/8/04, pages 4481-4482). Further, numerous prior art publications teach the use of recombinant adenovirus for at least transient expression of heterologous proteins, including cytokines, see for example U.S. Patent 6,399,587 (2002), Mehtali et al. which teaches adenoviruses encoding human IL-2 and the administration of recombinant adenovirus to mammals in dosages of between 10-6 and 10-12 pfu; however, none teach that "high" doses of recombinant adenovirus are capable of inhibiting antigen presenting cells or formation of neutralizing antibodies against a heterologous protein encoded by the recombinant adenovirus or administered separately in a different viral vector or as a soluble protein.

The rejection of record also discussed in detail the apparent difficulty in determining a dosage of recombinant adenovirus encoding a heterologous protein that can be "tolerizing" in a mouse. The specification discloses that the amount of recombinant adenovirus encoding a heterologous protein administered to a mammal determines whether it induces immunization or tolerization. The working examples, however, clearly demonstrate that there is no specific dose of adenovirus that is always "tolerizing" rather than "immunizing". The working examples show that different preparations of the same recombinant adenovirus, an adenovirus encoding human TPO (Ad-TPO), require the administration of different amounts of the virus to inhibit neutralizing antibody formation against TPO in mice. In one set of experiments, 6 X 10-9 pfu of Ad-TPO administered retro-orbitally to mice is immunizing and 8X10-9 pfu is "tolerizing", whereas in a second set of experiments 6X 10-9 pfu of Ad-TPO is "tolerizing". The working examples also teach that a second recombinant vector encoding beta-galactosidase required the

higher amount of 8X10-9 pfu for a "tolerizing dose". However, this experiment only states that "some" hepatocytes showed beta-gal expression after 5 months. It is unclear from these results whether neutralizing antibodies against beta-gal were in fact inhibited. Further, the specification acknowledges the unpredictable variability of the "tolerizing dose" stating that the tolerizing dose must be independently determined for each viral preparation. Consideration of the teachings of the specification in combination with the state of the prior art leads to the conclusion that the dosage of recombinant adenovirus capable of inhibiting neutralizing antibodies to an encoded heterologous protein cannot be determined for any given adenovirus encoding a particular heterologous protein, or for any particular preparation of adenovirus encoding a particular heterologous protein without experimentation to test a range of dosages for the "tolerizing" effect desired. Further, the particular examples utilizing intravenous injection of recombinant adenovirus encoding TPO disclosed in the specification and in the prior art of Abina et al. shows that even 6X10-9 pfu of a recombinant adenovirus encoding human TPO may not be adequate to inhibit neutralizing antibodies. It is also reiterated that the claims as written, with the exception of claims 23 and 26, are not limited to inhibiting neutralizing antibodies in mice. The claims read broadly on practicing the methods in any mammal, and further, with the exception of claims 17-18, broadly encompass the use of any route of administration not limited to intravenous or specifically retroorbital administration. The specification provides no specific guidance for dosages of recombinant adenovirus encoding any heterologous protein, including a cytokine, which are capable of depleting or inhibiting antigen presenting cells leading to inhibition of neutralizing antibodies to the encoded heterologous protein when administered by any route of

administration to any mammal including goats, cows, sheep, rabbits, horses, or primates including humans.

Therefore, as discussed in detail above and in the previous office action, the teachings of the specification and the working examples demonstrate the unpredictability in determining the "tolerizing dose" of recombinant adenovirus encoding the heterologous protein *a priori*, even between different batches of the same virus. This unpredictability in achieving tolerance versus immunization is further increased by the limitation of the working examples to a single route of administration, intravenous, and by the use of a single recombinant vector which encodes the heterologous protein. In view of the large body of work in the prior art using both wild type and recombinant adenoviruses, where neutralizing antibodies were formed over a large range of doses and using different routes of administration, the skilled artisan would not have been able to predict without undue experimentation whether the applicant's successful demonstration of transient tolerance with a single recombinant adenovirus, at a dosage in one experiment which the prior art teaches to be immunizing not tolerizing, could be extrapolated to any recombinant adenovirus encoding any cytokine and any route of administration, or to the administration of a recombinant adenovirus and a second recombinant virus or protein, either simultaneously or not, using any route or routes of administration. As such, in view of the state of the art of adenovirus induction of neutralizing antibodies at the time of filing, the breadth of the claims, the limited disclosure in the specification and working examples, and the unpredictability as demonstrated by both the prior art and the working examples for using adenovirus to inhibit rather than induce neutralizing antibodies, it would have required undue experimentation to practice the invention as claimed.

It is further noted that the declaration, in addition to discussing the specification, offers a description of a "typical" experiment which may be performed based on the teachings in the specification. It is noted that no actual experiments in addition to the ones disclosed in the specification are provided. The "typical" experiment described in the declaration refers to the use of one to 10 "mutants", depending on the target antigenicity and protein length, each one in an adenovirus construction with a promoter as described on page 23 of the specification, where the mutation should maintain a homology of 75%-95%, where 3-4 dosages of the viruses should be 6X 10-9, 8X10-9, 9X10-9 and 10-10 as disclosed in page 20 of the specification. However, such an experiment as described by the declaration is not reflected in the claims as written. It is also noted that none of the experimental data provided utilizes mutant proteins. Thus, the "typical" experiment discussed by the declaration is not commensurate in scope with the claims as written.

Finally, the declaration refers to publications by Wucherpfennig et al., Zhao et al. Panoutsakopoulou et al. and Levin et al., copies of which were provided for consideration by the examiner. The relevance of these publications to the issues raised in the enablement rejection is not clear. These publications are all drawn to the subject of molecular mimicry between viral proteins and self-proteins in which viral injection is posited to induce autoimmunity. However, molecular mimicry and the role of viruses in autoimmune disease is not relevant to the enablement of the methods as claimed which are drawn to inhibiting neutralizing antibodies against heterologous protein encoded by a recombinant adenovirus. None of the cited references are drawn to this subject matter. As such, the teachings of Wucherpfennig et al., Zhao et al. Panoutsakopoulou et al. and Levin et al. are not persuasive in overcoming the rejection of record.

Therefore, the rejection of record stands.

Applicant's amendment has necessitated the following new grounds of rejection.

Claim 38 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 38 recites the method of claim 19 wherein the administration of the recombinant adenovirus to the mammal "causes a specific phenotypic results" in the mammal, measurable by molecular assays or clinical markers. The specification fails to provide sufficient written description for the genus of "specific phenotypic results" encompassed by the claims.

As an initial matter, the methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The specification fails to adequately describe the genus of "specific phenotypic results" resulting from administration of recombinant adenovirus encoding a heterologous protein as claimed. The only discussion of phenotypes in the specification occurs on page 28, which states that a dosage of "agent and heterologous protein" is to be chosen which causes a specific phenotypic result. The only example of such as phenotype described by the specification is transgene expression. The specification does not describe any other phenotype or "specific phenotypic result" resulting from administration of an adenovirus encoding a heterologous protein. Thus, the specification fails to set forth in terms of distinguishing identifying characteristics as evidenced by descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the genus of specific phenotypic results capable of being measured by molecular assays or clinical markers other than transgene expression.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or

structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of measuring any specific phenotypic results other than transgene expression. Based on the applicant's specification, the skilled artisan cannot envision measurable or assayable "phenotypes" resulting from adenovirus administration. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Thus, for the reasons outlined above, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention because it does not provide adequate written description for the genus of measurable/assayable specific phenotypic results in any mammal caused by administration of a recombinant adenovirus encoding a heterologous protein.

The rejection of claims 4, 11, and 19-26 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the amendments to claims 4, 11, and 19, and the cancellation of claims 20-22 and 24-25.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633